Remarks

Claims 1-26, 29-49 and 59-68 are pending in the present application. Favorable reconsideration of the claims is respectfully requested. Applicants have hereinabove-cancelled claims 2-5, 11, 15-26, 30-33 and 40-43 without prejudice to applicants' right to pursue patent protection for the cancelled subject matter in a later filed divisional or continuation application. Applicants have previously canceled claims 27, 28 and 50-58 in the March 24, 2003 Amendment filed in response to the November 22, 2003 Office Action. Applicants have hereinabove amended claims 1, 6, 12, 13, 29, 34, 39, and 44. Applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment the pending claims are 1, 6-10, 12-14, 29, 34-39, 44-49, and 59-68.

Applicants elected in their October 21, 2002 response to a Restriction Requirement to prosecute claims 1-49 of Group I in this application, wherein X is CH and Y is N. On page 2 of the April 18, 2003 Action the Examiner stated that the amended claims were objected to as still containing non-elected subject matter that was withdrawn from consideration. Applicants have hereinabove amended the claims of the subject application to read upon the elected subject matter of Group I, claims 1-49, wherein X is CH and Y is N.

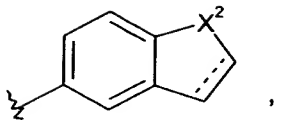
Applicants have not canceled non-elected method of use claims 59-68 since they are drawn to subject matter which is eligible for rejoinder pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86). Also see M.P.E.P.. § 821.04 "Rejoinder". Claims directed to process for making and/or using the product, which depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance. Id. In order to expedite prosecution M.P.E.P. § 821.04 recommends that applicants present rejoinder claims, preferably as dependent claims, in the application at an early stage of prosecution. Id. Applicants respectfully submit that rejoinder is applicable for the method of use claims 59-68. Applicants originally elected to have claims 1-49 examined first. Method of use claims 59-68 are written in dependent form as suggested in M.P.E.P. §821.04 for rejoinder to the product claims. Applicants respectfully request that claims 59-68 be rejoined with the pending product claims and fully examined for patentability under 37 C.F.R. § 1.104.

I. Enablement Rejection Under 35 U.S.C. §112, first paragraph for Claims 1-12, 15-26 and 49

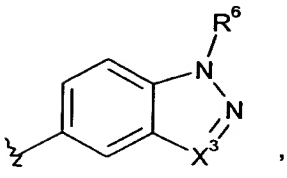
On page 2 of the April 18, 2003 Action the Examiner maintained his rejection of claims 1-12, 15-26 and 49 under 35 U.S.C. §112, first paragraph, as allegedly not been enabled for the preparation and use of compounds wherein R^2 is a functional group other than indole or quinoline. The Examiner asserts that the specification does not enable any person skilled in the art to which it pertains, or with which it is mostly nearly connected, to practice the claimed invention commensurate in scope with the claims. Applicants respectfully traverse this position for the following reasons.

Applicants do not concede that the rejected claims of the subject application are not enabled, however, in the interest of expediting the prosecution of the subject application applicants have hereinabove amended claim 1 of the subject application by incorporating the definition of R^2 from dependent claim 11. Accordingly, the definition of R^2 for the subject application has been limited to ring systems with bicyclic and tricyclic ring systems. The Examiner of the subject application acknowledged in her November 22, 2002 Office Action that the claims of the subject application were enabled for indole and quinoline ring systems. Applicants respectfully submit that the incorporation of the subject matter of bicyclic and tricyclic ring systems claimed in claim 11 is enabled by the subject application. The subject matter from claim 11, which has been incorporated into claim 1, is shown below for the convenience of the Examiner:

"R^2 is a group of the formula



2



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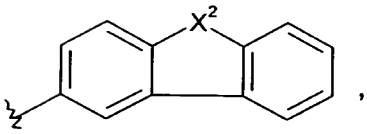
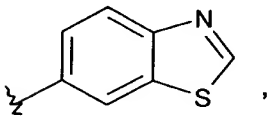
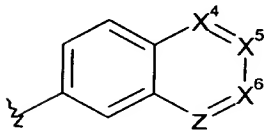


4



5

or



6

wherein X^2 is -S-, -N(R^6)- or O, and X^3, X^4, X^5, X^6, and Z is N or CH, the dashed line in formula **2** represents an optional double bond, and the above R^2 groups of formulas **2, 4** and **6** are optionally substituted by 1 to 5 R^5 substituents and the R^2 groups of formulas **3** and **5** are optionally substituted by 1 to 3 R^5 substituents"

Applicants also hereby incorporated by reference their detailed remarks from the their March 24, 2003 Amended in response to the November 22, 2003 Office Action on pages 3-9 concerning the teachings applicants provided of the method of making and using the compounds of the claimed invention in the treatment of hyperproliferative disorders, such as cancer. Applicants respectfully submit that the claims and specification of the present application meet the enablement requirement of §112, first paragraph. Accordingly, applicants respectfully request that the Examiner withdraw the rejection of claims under §112, first paragraph.

II. Enablement Rejection Under 35 U.S.C. §112, first paragraph for Claims 1 and 15

On page 4 of the Action the Examiner maintained his rejection of the use of the term "prodrug" in claims 1 and 15 under §112, first paragraph for the reasons of record. The Examiner stated that applicants' argument that the specification provides a definition for the term "prodrug" on pages 17 and 18 could not be found. The Examiner further states that the term is still too broad to enable one skilled in the art to determine how the prodrug is converted to active compounds, by what mechanisms and what site the prodrug will be active, what in vivo enzymes are likely to be involved in cleaving the protected group. The Examiner concludes that all these factors are uncertain and require one skilled in the art to spend undue amount of time to practice the invention. Applicants respectfully disagree with the Examiner's position and the Examiner's flawed logic in rendering a §112, first paragraph enablement rejection for the following reasons.

In view of the cancellation of claim 15 hereinabove this rejection is rendered moot for that claim.

10/227,193

Applicants incorporated by reference their detailed remarks from the March 24, 2003 Amended in response to the November 22, 2003 Office Action on pages 10 to 12.

Applicants again reiterate that term "prodrug" is well-known and familiar term to those of ordinary skill for the instant invention. As previously reference applicants have also provided a detailed explanation of prodrugs and methods to make them on page 17, lines 16 to 36 of the subject application. Applicants understand that the Examiner was unable to find the definition of "prodrug" in the subject application. Applicants have hereinbelow excerpted the definition of prodrug from pages 17 and 18 of the subject application for the Examiner's convenience:

> Compounds of formula **1** having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of formula **1**. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone.

> Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews*, **1996**, *19*, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* **1996**, *39*, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

Applicants have provided a detailed explanation of the term "prodrug" in the specification of the subject application. The Examiner states that the applicants' do not "enable one skilled in the art to determine how the prodrug is converted into active compounds." Applicants respectfully submit that they are not required to provide those of ordinary skill in the art with a blueprint document for concepts that are well understood by those of ordinary skill in the art.

It is well understood, recognized, appreciated, and accepted in the art that chemical compounds, such as formula **1**, having free amino, amido, hydroxy or carboxylic groups can be readily converted into prodrugs. Applicants are not required to teach what is well understood and accepted practice. The Examiner is providing summary conclusions without any underlying reasoning why he believes that the preparation and use of prodrugs from the compounds of the present invention could not be practiced by those of ordinary skill in the art.

Furthermore, as applicants stated in their previous response (March 24, 2003 Amendment), the present Examiner (and Supervisory Patent Examiner) of the instant application has issued patents containing the apparently rejected claim language "prodrug" on number of occasions in the recent past. See, U.S. Patent No. 6,486,185 (use of the term "prodrug" at least 12 times in the claims with a general explanation of the term "produg" in column 4, lines 5-20); and U.S. Patent No. 6,369,226 (use of the term "***prodrug***" in the issued

claims with a very short standard definition of the term "prodrug" in the detailed description of the invention as "a compound that is converted under physiological conditions or by solvolysis or metabolically to a specified compound that is pharmaceutically active.").

Applicants respectfully submit that the term "prodrug" is a term of art that no detailed explanation of the term in the specification is required as shown by the issuance of claims in the aforementioned patents. Nevertheless, for the sake of clarity and completeness applicants of the present application have provided a detailed explanation of the term "prodrug". Nothing further is required. Accordingly, applicants respectfully request that the Examiner withdraw his rejection of claim 1 under 35 U.S.C. §112, first paragraph in view of the preceding remarks.

III. Rejections under 35 U.S.C. §112, Second Paragraph

On pages 4 and 5 of the Action the Examiner maintains his rejection of 1-4, 15-18, 30-32 and 40-42 under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated in the November 22, 2002 Office Action that use of the term "heterocyclic" and "heterocyclic" in claims 1-4, 15-18, 30-32 and 40-42 is unclear to the array of heteroatoms, ring size, as well as the nature of atoms as ring members.

Applicants respectfully submit that the rejection of claims 2-4, 15-18, 27, 28, 30-32 and 40-42 are rendered moot in view of applicants' cancellation of the aforementioned claims hereinabove.

Applicants respectfully traverse the Examiner's rejection of claim 1 under 35 U.S.C. §112, second paragraph and respectfully request that it be withdrawn in view of the following remarks.

Applicants reiterate that the legal standard for determining whether particular claim language is sufficiently "definite" depends on whether one skilled in would understand the scope of that claim language when read in light of the patent specification. See, *Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 USPQ2d 1081 (Fed. Cir. 1986); Seattle Box Co. v. Industrial Crating & Packing Inc., 221 USPQ 568, 574 (Fed. Cir. 1984); In re Morasi, 218 USPQ 289, 292 (Fed. Cir. 1983).*

Applicants respectfully submit that the definition of the term "heterocyclic" is patently

clear to one of ordinary skill in the art based upon applicants' disclosure, as well as the voluminous information on heterocyclics in the art. Applicants provided on page 17, lines 5-27, a clear definition of term "heterocyclic." As defined by applicants a heterocyclic means an aromatic or non-aromatic heterocyclic group containing one to four heteroatoms each selected from O, S, and N, i.e., at least one heteroatom is present. Furthermore, applicants provided a long list of representative examples of heterocyclics on page 17 of the subject application.

The term "heterocyclic" is a well-known term used frequently by those of ordinary skill in the art. As such it is readily understandable to those of ordinary skill in the art. One skilled in the art readily recognizes that a heterocyclic as defined by applicants, and as known in the art, requires the presence of at least one heteroatom in order to be considered a heterocyclic. Applicants respectfully submit that one of ordinary skill in the art reading the claims of the subject application in view of the accompanying specification and the teachings of the prior art would understand what is claimed. Accordingly, applicants respectfully submit that they have provided an adequate and clear disclosure for the term "heterocyclic" and this disclosure coupled with the extensive teachings in the prior art, satisfies the requirements for the second paragraph of section 112.

Furthermore, applicants note that the Court of Appeals for the Federal Circuit in *Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 225 USPQ 634 (Fed. Cir. 1985)*, stated:

> "The amount of detail required to be included in claims depends on the particular invention and the prior art, and is not to be viewed in the abstract but in conjunction with whether the specification is in compliance with the first paragraph of section 112: "If the claims, read in the light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." (emphasis added)(citations omitted)."

Applicants respectfully submit that one of ordinary skill in the art would easily be able to determine the appropriate heteroatoms, ring size, as well as the nature of atoms as ring members. The term "heterocyclic" is a well-established and understood term of art in the

pharmaceutical arts.

Patent law does not require that all possible heteroatoms, ring sizes as well as the nature of the ring members be listed in the patent, let alone that they be listed in the claims.

A determination of whether a claim satisfies Section 112, second paragraph is a determination of whether those of skilled in the art would understand what is claimed when the claim is read in light of the specification and what is well-known in the art. Interpretation of claim language is not done in a vacuum. As stated above in the excerpt from the Federal Circuits decision on Shatterproof Glass "if the claims, read in the light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." Applicants respectfully submit that the courts can demand no more of applicants nor can the patent office.

Once again applicants respectfully submit that the term "heterocyclic" is not only well understood by those of ordinary skill in the art but also by the Examiner and Supervisory Patent Examiner of the present application. A simple search of the USPTO patent literature identifies patents with claims with the term "heterocyclic" issued by the Examiner and Supervisory Patent Examiner of the instant application. Applicants are at a loss for rationale behind the issuance of second paragraph 112 rejection over a term which is not only well understood and accepted by those of ordinary skill in the art but also well understood and part of the art recognized by the Examiners of the instant application.

Applicants direct the Examiners attention to the following U.S. patents which include claims with the apparently indefinite term "hereocyclic" issued by the Examiners of the instant application: 6,518,286 (term "heterocyclic" in claims with no definition of heterocyclic in the specification); and 6,469,014 (term "heterocyclic" in claims with no definition of heterocyclic in the specification). Applicants respectfully request the Examiner provide an explanation why he believes applicants use of the term "heterocyclic" is different from those in the patents he has issued in the recent past.

Applicants remind that Examiner *unlike* the aforementioned patents that they have provided a detailed explanation in the specification of the instant application with examples of the term "heterocyclic". Applicants respectfully submit that the term "heterocyclic" is a term of art well understood by those of ordinary skill in the art. Applicants are not required to

provide the patent office with a production manual. Accordingly, applicants respectfully request that the Examiner withdraw his 112 second paragraph rejection of claim 1 in view of the preceding remarks.

IV. Rejection under 35 U.S.C. §103(a)

The Examiner maintained his rejection of claims 1-26 and 29-49 under 35 U.S.C. §103(a) as allegedly being unpatentable over WO 1999/24440 (Munchhof et al.). The Examiner states that he is not able to see any "contrast" between the definition of R^{12} and R^{13} in substituent R^{11} to R^6 and R^7 of the '440 application. The Examiner asserts that applicants' claims are deemed to be encompassed by the reference and thus maintains his rejection.

Applicants respectfully submit that the rejection is moot for claims 2-5, 11, 15-26, 30-33, and 40-43 in view of their cancellation hereinabove.

Applicants respectfully traverse the Examiner's rejection of claims 1, 6-10, 12-14, 29, 34-39, and 44-49 in view of the amendment of independent claim 1 and the following remarks.

In the interest of expediting prosecution of the subject application applicants have hereinabove amended the definition of R^{11} of independent claim 1 by incorporating the dependent definition from claim 5 shown below:

> R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring are optionally substituted by 1 to 5 R^5 substituents.

Applicants respectfully submit that there is no teaching or suggestion in Munchhof to motive one ordinary skill in the art to make compounds of formula 1 wherein R^{11} is $-C(O)NR^{12}R^{13}$ wherein R^{12} and R^{13} taken together with the nitrogen to which they are attached form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl,

pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl ring are optionally substituted by 1 to 5 R^5 substituents. Applicants' respectfully submit that such a motivation does not exist *except* in the presence of applicants' disclosure.

Applicants respectfully submit that Muchhoff et al. disclosure does not embrace applicants claimed invention. Munchhof et al. defines the equivalent substituent R^{11} as follows:

> R^{11} is H, C_1-C_6 alkyl, -C(O)NR^6R^9, -C(O)(C_6-C_{10} aryl), -$(CH_2)_t$(C_6-C_{10} aryl), or -$(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer ranging from 0 to 6, wherein said R^{11} groups, other than H, are optionally substituted by 1 to 5 R^5 groups;

Applicants respectfully submit that there is not teaching or suggestion in Munchhof et al. which would lead one to the presently claimed invention. Accordingly, applicants' respectfully submit that the motivation requirement for a *prima facie* case of obviousness is not present. Some motivation to select the claimed species or subgenus must be taught by the prior art. See, e.g. *In re Deul, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).* Arriving at the claimed invention in the absence of the necessary motivation cannot be used to establish a *prima facie* case of obviousness. Accordingly, applicants respectfully request that the Examiner withdraw his rejection of claims under 35 U.S.C. §103(a) over Munchhof et al.

Conclusion

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for rejection set forth in the April 18, 2003 Office Action and earnestly solicit allowance of the claims pending in the subject application.

Respectfully submitted,

Date: October 13, 2003

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